Use of certain contrast agents with MR is known in the art. Contrast agents are commonly used intravenously to change the local magnetic field in tissue. Generally, abnormal tissue will respond differently in the presence of the contrast agent as compared to normal tissue and will give off a different magnetic echo. Thus, when the magnetic echoes are translated into an image, an image of the tissue abnormalities is provided.

The use of gadolinium oxide (Gd_2O_3) particles alone measuring less than 2 micrometers (μm) in diameter as a prototype MR contrast agent has been examined for imaging the liver and spleen. (Burnett et al., "Gadolinium Oxide: A Prototype Agent for Contrast Enhanced Imaging of the Liver and Spleen with Magnetic Resonance," *Magnetic Resonance Imaging*, 3:65-71 (1985)).

Another study evaluated the effects of gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA), albumin Gd-DTPA, and Gd_2O_3 on imaging of the spleen and renal cortex. (Daly et al., "MR Image Time-Intensity Relations in Spleen and Kidney: A Comparative Study Of GdDTPA, Albumin-(GdDTPA), And Gd_2O_3 Colloid," *American Journal of Physiologic Imaging*, 5:119-24 (1990)). The suspension of Gd_2O_3 used in the studies by Burnett and Daly was synthesized by titrating a $GdCl_3$ solution with NaOH. With this method of preparation, residual $GdCl_3$ is likely to remain in the Gd_2O_3 preparation, such that extreme toxicity from inadvertently incorporated free $GdCl_3$ is possible. With most chelated gadolinium contrast agents, only one gadolinium atom per molecule is present in commercially-available contrast media manufactured for use in MR imaging, so that the enhancement capabilities of the contrast agent are limited. In addition, synthesis of albumin particles and also albumin microspheres tagged with gadolinium chelates on the surface

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would also be expected to have decreased MR sensitivity due to the limited number of sites for conjugation of the gadolinium chelate to the microsphere surface.

Magnetite (Fe_3O_4) albumin microspheres ("MAM") have been used as a superparamagnetic contrast agent for reticuloendothelial MR imaging. (Widder et al., "Magnetite Albumin Suspension: A Superparamagnetic Oral MR Contrast Agent," *ARJ,* 149: 839-43 (1987)). MAM was synthesized by combining 5% human serum albumin ("HSA") and magnetite to create albumin microspheres using a modified water-in-oil emulsion polymerization technique. Nonlinear behavior of MAM with increased applied external magnetic field over 0.3-0.9T was observed. The influence of magnetite on T_2 relaxation is believed to be due to local field inhomogeneities generated by the large magnetic moment of Fe_3O_4, which causes dephasing of proton spins and an acceleration of T_2 relaxation with negligible T_1 effects. Because iron oxide is predominately a T_2 relaxation agent, MAM has limited usefulness in conventional MR imaging. Additionally, based on the lower density of iron oxide relative to other heavy metals, iron oxide, and thus MAM, has a very limited utility for other imaging modalities, such as computed tomography.

As with contrast agents for US, contrast agents for MR also have limitations, both when used with MR and if used with other imaging modalities. Few MR contrast agents have even been evaluated for use with other imaging modalities.

Computed Tomography

Computed tomography ("CT"), also called computerized axial tomography, is an imaging modality that utilizes a toroidal, or donut-shaped x-ray camera to provide a cross-sectional image of the body area of interest. Use of certain contrast agents to improve CT

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images is known. Generally, the contrast agent localizes in a particular body compartment and differentially opacifies normal or abnormal tissue. The contrast agent causes the tissue to inhibit passage of x-rays to produce a shadow of positive contrast in the resulting image. Iodine-based contrast agents are considered to be the industry standard with CT.

Gd-DTPA contrast agents have been used for certain limited applications in conventional angiography and CT imaging. (Bloem and Wondergem, "Gd-DTPA as a Contrast Agent in CT," *Radiology*, 171:578-79 (1989)). A major drawback associated with using Gd-DTPA contrast agents for CT imaging is the fact that only one electron dense (gadolinium) atom per molecule is present in commercially-available contrast media. In comparison, two widely used contrast agents, Optiray® (by Mallinckrodt, Inc., of St. Louis, MO) and Ultravist 300® (by Berlex Laboratories, Inc., of Wayne and Montville, NJ and Richmond, CA), contain three electron dense (iodine) atoms per molecule. In addition, the molar concentration of gadolinium in commercially-available gadolinium-based contrast agents, such as Magnevist® (by Berlex Laboratories, Inc., of Wayne and Montville, NJ and Richmond, CA), is 0.5 mol/L, which is one-fifth the molar concentration of iodine in Optiray® (320 mg of iodine per mL, or 2.5 mol of iodine per liter). Thus, presently available MR contrast agents provide sub-optimal CT enhancement and/or are not well-suited for use with other imaging modalities, such as CT and US.

Study Of Contrast Agents In Different Imaging Modalities

To date, few contrast agents have been used for imaging studies utilizing multiple imaging modalities. Correlative studies using combinations of imaging methods, most notably CT and MR imaging, are frequently performed in order to improve the accuracy of

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